Click reaction in supercritical carbon dioxide: towards the synthesis of functional polymers in a green medium

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INTRODUCTION.

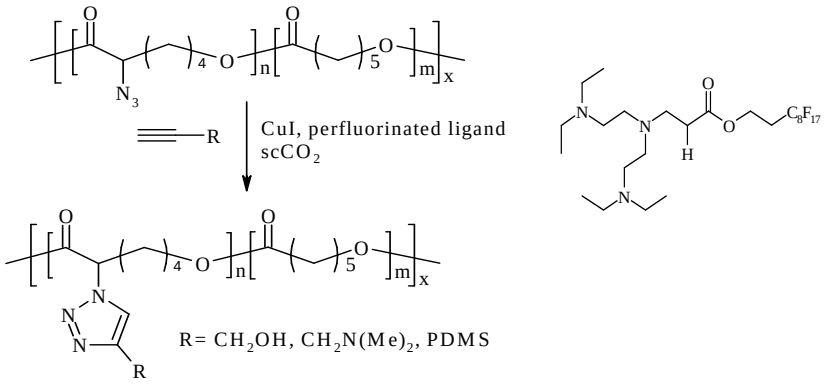
Since the pioneering work of Meldal *et al.* and Sharpless *et al.*, the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC), which is nothing but the most popular "click reaction" , has been the subject of extensive researches in the very recent years for the development of macromolecular engineering. This interest relies on the major benefits related to the CuAAC reaction, i.e. its versatility, high yields, stereospecificity, and the absence of undesirable by-products after reaction. Up to now, most of the works focused on the CuAAC reaction in aqueous or in organic media. In this contribution, we report the first examples of CuAAC "click reaction" in $scCO_2$. The concept was first developed for the functionalization of biodegradable and biocompatible aliphatic polyesters. Due to the low critical parameters of CO_2, i.e. Tc= 31.2°C and Pc = 73.8 bar, the CuAAC reaction was performed under mild conditions limiting any degradation risks for the polyester. In a second step, polymer purification by supercritical fluid extraction of the copper catalyst is also discussed, leading to functional polyesters with low catalytic residues. Subsequently, because both CuAAC and Atom Transfer Radical Polymerization (ATRP), that is one of the most robust tool for the preparation of polymers with well-defined molecular weight, architecture and chain-end functionality, rely on the use of a Cu(I) catalyst, the concept was extended to the synthesis of functional polymers by the combination in a one-pot process of CuAAc and dispersion ATRP of MMA. Indeed, despite a huge number of works dealing with combination of ATRP and click reaction, examples of simultaneous or one-pot ATRP and click is quite limited. So, the combination of these two techniques in a one-pot process showed to be an attractive approach.

MATERIALS AND METHODS. CuBr (Aldrich, 98%) was purified by dispersion within glacial acetic acid under stirring for a few hours, filtered, washed with ethanol, dried under reduced pressure at 80°C and stored under nitrogen. Methyl methacrylate (MMA, Aldrich 99%). 1H,1H,2H,2H-heptadecafluorodecyl-3-(bis(2-(diethylamino)ethyl)amino)propanoate was prepared by Michael addition at 50°C for 24h in methanol using equimolar amount of 1H,1H,2H,2H-heptadecafluorodecylacrylate and tetraethyldiethylenetriamine [1]. All the others reactants were used as received. The fluorinated macroligand and azido-functional aliphatic polyesters [3,4] were synthesized as reported elsewhere. Size exclusion chromatography (SEC) was performed in THF at 45°C with a flow rate of 1ml/min using a SDF S5200 autosampler liquid chromatograph equipped with SDF refractometer index detector 2000. Columns (HP PL gel 5µm; 10^5 Å, 10^4 Å, 10^3 Å, 100Å) were calibrated with poly(methyl methacrylate) standards.

RESULTS

Functionalization of aliphatic polyesters. Well-defined azido-functional aliphatic polyesters were recently prepared by our group according to a two-step strategy relying first on the random copolymerization by ring opening polymerization of α-chloro-ε-caprolactone

(αClεCL) with ε-caprolactone (εCL) using a tin alkoxide, i.e. dimethoxydibutyl tin, as an initiator [3]. In a second step, the pendant chlorine groups were quantitatively converted into azides by nucleophilic substitution with NaN_3. The heterogeneous CuAAC reaction between the CO_2-phobic (poly(εCL-*co*-αN_3CL) and prop-2-yn-1-ol, *N*,*N*-dimethylprop-2-yn-1-amine or alkyne end-functionalized PDMS was then investigated in $scCO_2$ (Scheme 1) using copper iodide as a catalyst complexed by a perfluorinated ligand, i.e. 1H,1H,2H,2H-heptadecafluorodecyl-3-(bis(2-(diethylamino)ethyl)amino)propanoate.



Scheme 1: Modification of poly(εCL-*co*-αN_3εCL) random copolyesters with different alkynes by the CuAAC reaction in $scCO_2$

Prop-2-yn-1-ol was first grafted onto poly(αN_3εCL-*co*-εCL) (30 mol% of αN_3εCL, Mn = 10000 g/mol). Under suitable experimental conditions, ^{1}H NMR analysis of the resulting polymer confirmed that the CuAAC went to completion in $scCO_2$ even though the aliphatic polyester was not soluble and despite the high dilution of the medium. This remarkable result can be accounted for by the exceptional mass transport properties and the diffusivity of $scCO_2$ comparable to those of gases. Consequently, the diffusion of prop-2-yn-1-ol into the very well plasticized poly(αN_3εCL-*co*-εCL) matrix was rapid and the CuAAC reaction was fast and quantitative whatever the location of the azides. Interestingly enough, the functionalization of the polymer proceeds without any degradation as evidenced by a narrow and monomodal molecular weight distribution. For sake of comparison, when the same reaction is repeated in the same conditions but using THF as a solvent, a slight degradation was observed.

The effect of the catalyst content on the reaction kinetics was also investigated. The same experiments were repeated with 5% of CuI (instead of 10% compared to the alkyne) or without addition of copper iodide while keeping all the others reaction parameters constant. When 5% of catalyst was used, the grafting yield decreased to 81% whereas no reaction occurred without CuI.

In a next step, the CuAAc was extended to the coupling of other substituted alkynes such as *N*,*N*-dimethylprop-2-yn-1-amine or alkyne-terminated PDMS onto the same poly(αN_3εCL-*co*-εCL) (30 mol% of αN_3εCL, Mn = 10000 g/mol). Conditions for successful reaction will be discussed in detail during the presentation.

Finally, the purification of the functionalized aliphatic polyesters from the residual copper salt by supercritical fluid extraction will be reported. We will demonstrate that, upon optimal conditions, 96% of the catalyst can be easily removed.

One-pot CuAAc and dispersion ATRP. Successful synthesis of polymethylmethacrylate (PMMA) and polystyrene (Psty) particles by dispersion ATRP in $scCO_2$ was recently reported

by our group using perfluorinated amino-macroligands that had a dual role, i.e. the complexation of the copper (I) catalyst and the stabilization of the polymeric growing particles [5,6] Dispersion ATRP of MMA and styrene were shown to be controlled and livingness of the MMA polymerization was demonstrated by the MMA resumption and the synthesis of poly(methyl methacrylate-b-2,2,2-trifluorethyl methacrylate) diblock copolymer, polymers that were collected as microspheres[5]. On the basis of these results, the preparation of functional PMMA in a one-pot process by combination of CuAAc and dispersion ATRP was considered. For this reason, an azido functional ATRP initiator was first prepared and considered for the functionalization of PMMA. From this study, it appears that when the ATRP of MMA was conducted at 60°C using the suitable catalytic system, the monomer conversion was high (> 90%), the experimental molecular weight was in good agreement with the theoretical value, the polydispersity was narrow ($M_w/M_n < 1.25$) and PMMA-N_3 was collected as small-sized microspheres with a diameter between 10 and 20 µm.

In a next step, functionalization of PMMA by the one-pot CuAAc and dispersion ATRP strategy was investigated using the same azido functional ATRP initiator and a pyrene bearing an alkyne group for the click reaction. In optimal conditions, after depressurisation of the high pressure cell, PMMA functionalized by pyrene at the α-chain end was collected as small size microspheres with a diameter between 10 and 20 nm. The presence of the pyrene moiety at the chain-end, and thus the successful click reaction, was evidenced by fluorescence microscopy and GPC with UV detection.

CONCLUSIONS.

Copper(I) catalyzed azide-alkyne cycloaddition of Huisgen has been successfully implemented in $scCO_2$ for the first time. The concept was first applied for the functionalization of aliphatic polyesters by alcohol or amino groups under mild conditions before being successfully extended to the synthesis of functional polymers by the combination of CuAAc and dispersion ATRP in one-pot approach.

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